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COMMENTARY

Small animal image-guided radiotherapy: status, considerations and potential for translational impact

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ABSTRACT

Radiation biology is being transformed by the implementation of small animal image-guided precision radiotherapy into pre-clinical research programmes worldwide. We report on the current status and developments of the small animal radiotherapy field, suggest criteria for the design and execution of effective studies and contend that this powerful emerging technology, used in combination with relevant small animal models, holds much promise for translational impact in radiation oncology.

STATUS

Over the past two decades, significant advances in radiotherapy technology have enabled increasingly sophisticated methods for treatment planning, delivery and imaging to be implemented into routine radiation oncology practice. As such, innovations in radiotherapy can be attributed primarily to technological developments rather than a more comprehensive understanding of the radiobiology underpinning responses in tumour and normal tissue that can be achieved through validation in animal models. Accurate simulation of the spatial and temporal complexity of dose typically delivered during contemporary radiotherapy techniques, such as intensity-modulated radiotherapy, is likely to facilitate a more thorough understanding of the biological basis of tissue responses to radiotherapy.

The recent development and commercialization of small animal image-guided radiotherapy devices is revolutionizing radiobiology research. Researchers are now empowered to conduct pre-clinical investigations in a manner that more accurately reflects the clinical scenario using millimetre-sized beams under precision cone beam CT (CBCT) image guidance.[1] The technology has much potential to address some of the current outstanding challenges in radiation oncology towards biological individualization, dose painting, adaptive radiotherapy and synergy with other treatment modalities. These were topics for discussion at the second symposium on precision image-guided small animal radiotherapy held recently from 11 to 13 August 2014 at the University of British Columbia, Vancouver, Canada.[2]

In addition to research reports from investigators around the world, the system manufacturers who share the small animal radiotherapy market also showcased their ongoing developments for their respective systems, the Xstrahl Life Sciences (Camberly, UK), Small Animal Radiation Research Platform, and the Precision X-ray Inc. (North Branford, CT), X-RAD 225Cx. Both systems are offering integrated precision irradiation with CBCT guidance and bioluminescence tomography for improved targeting and longitudinal response monitoring. They also offer treatment planning systems with dose calculation tools based on advanced superposition convolution (Muriplan from Xstrahl Life Sciences) or Monte Carlo methods (SmART-Plan from Precision X-ray Inc.).[3,4] Both companies continue to focus developments on more accurately reproducing the clinical scenario. Xstrahl, in collaboration with researchers at the Johns Hopkins University, Baltimore, MD, has developed a motorized variable radiation field collimator that will potentially allow delivery of intensity-modulated beams and a motion compensation shutter for beam gating during the respiratory cycle. Precision X-ray Inc., in collaboration with researchers at the University of Toronto, Toronto, ON, Canada, and the Maastro Clinic, Maastricht, Netherlands, is developing inverse dose planning techniques to allow delivery of more complex dose distributions with ease.

CONSIDERATIONS

The implementation of small animal radiotherapy into laboratory practice is essentially defining the emerging discipline of pre-clinical radiotherapy; allowing *in vivo* radiobiological studies to be performed in a manner highly analogous to clinical practice. A major challenge now facing investigators in the field is how to correctly apply the technology using relevant small animal models so that it can be leveraged to address the pertinent outstanding problems in radiation oncology. To do so effectively, a number of important criteria should be considered and applied to hypothesis-driven investigations using small animal radiotherapy. These criteria include:

Multidisciplinary study design and high-quality assurance

In the same way that the best course of treatment for a patient is determined through a multidisciplinary team meeting, pre-clinical investigations should be designed in a similar manner involving discussions between biologists, physicists and clinicians. A team-based approach will ensure that relevant strategies are adopted early in the design of studies, maximizing the potential for successful execution in the laboratory. Similar to radiotherapy in humans, irradiation of small animals should also be subject to strict quality assurance protocols. Beam accuracy can be verified using the on-board imaging devices that have shown small animal radiotherapy treatment plans to be delivered according to prescription within an uncertainty of 5% for beams as small as 4 mm in diameter.[5] However, there are currently no systematic quality assurance standards for pre-clinical radiotherapy, an area of concern being addressed internationally by the National Institute of Standards and Technology, the American Association of Physicists in Medicine and the National Cancer Research Institute Clinical and Translational Radiotherapy Research working groups.

Biologically relevant processes that mimic human conditions

Small animal radiotherapy studies should use models that are biologically relevant and that as far as possible recapitulate the physiological and pathological features of the clinical condition in humans. Tumour models established either spontaneously by mouse genome editing approaches or by xenografting have respective merits depending on the aims of the investigation.[6] Whilst orthotopic implantation is more technically challenging, it is significantly more representative of tumour biology than grafting to ectopic sites, particularly in the context of the tumour microenvironment. Irrespective of how an experimental model is established, it should be used with pre-defined, clinically relevant end points that will provide the data necessary to test key research hypotheses. Furthermore, it may be necessary to use several complementary models that focus on different aspects of underlying biological processes before drawing accurate evidence-based conclusions from a study.

Clinically relevant doses and fractionation schedule

Defining the dose–response relationship for tumour and normal tissues in mice is challenging. Classical radiobiological studies used the $LD_{50/30}$ end point, defined as the radiation dose resulting in death or survival of 50% of animals within 30 days. However, these measures may be confounded by both genetic (*e.g.* strain variation) and non-genetic factors (*e.g.* age, husbandry, microbial status). The human population is also heterogeneous in terms of radiosensitivity; therefore, direct comparison between mice and humans with certainty is difficult owing to multiple confounding factors. However, it is generally believed that dose effects in mice and humans are in fact comparable and so clinically relevant doses should be delivered in mice. The capability of precision guidance now enables the delivery of multiple fractions and so studies can deliver clinically relevant treatments in terms of both dose and fractionation schedule.

Relevance to human radiotherapy trials

The goal of pre-clinical radiotherapy studies is ultimately to translate discovery through human trials, therefore, pre-clinical radiotherapy studies should be designed to align with Phase 1 trials. Furthermore, small animal radiotherapy studies can be performed in parallel with human trials to gain *de novo* mechanistic insight into trial outcomes, an intriguing concept recently described by Abate-Shen and Pandolfi[7] for translational integration of mouse and human trials. The capacity to model human radiotherapy trials in mice is not a trivial task but has much potential to provide further radiobiological understanding and improve the basis upon which trials in humans are designed.

The above criteria highlight some of the important considerations for the design of effective small animal radiotherapy studies. These criteria are not comprehensive in scope, as there are many additional biological and technical issues to consider including choice of anaesthesia, number of animals needed to ensure statistical power in conclusions and the technical workflow from treatment planning through to tissue collection that should be considered when designing small animal radiotherapy studies.

POTENTIAL FOR TRANSLATIONAL IMPACT

Mouse models have been used extensively as the model of choice for pre-clinical research, as they share anatomical and genetic similarities with humans,[8] yet, only about a third of highly cited animal studies have translated at the level of human randomized trials.[9] In the context of radiotherapy clinical trials, patients recruited to experimental arms often may not have improved outcomes compared with the standard of care.[10] The reasons for these negative outcomes and the possible solutions to improve radiotherapy trials have been identified through the Radiation Research Programme of the National Cancer Institute.[11] Robust pre-clinical data accompanied with translational strategies are key factors to improving radiotherapy trial outcomes. Small animal radiotherapy offers the capacity to improve pre-clinical studies that will in turn facilitate better approaches for translation. In addition, there is a need for much collaboration across research centres, which may be best implemented through an international network to co-ordinate efforts and reduce the timeframe and associated research costs for translational development.

Despite the challenges, small animal radiotherapy has potential to bridge the translational gap between basic radiobiology and radiotherapy and presents a promising future. Pre-clinical data

in small animals must be interpreted correctly and with due consideration of the limitations. As researchers gain confidence in their roles as multidisciplinary scientists, pre-clinical studies will increasingly replicate the clinical scenario with unprecedented accuracy, driving new approaches in radiobiology that will ultimately translate to human health gains.

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